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ORIGINAL ARTICLE

Factors linked to longterm survival of patients with hepatocellular carcinoma accompanied by tumour thrombus in the major portal vein after surgical resection

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Abstract

Objectives: The prognosis in patients with hepatocellular carcinoma (HCC) accompanied by main portal vein tumour thrombus (MPVTT) is poor. The aim of this study was to clarify the factors linked to survival of >5 years after hepatectomy in HCC patients with MPVTT.

Methods: Twenty-nine HCC patients with MPVTT were divided into two groups comprising, respectively, patients who survived >5 years after hepatectomy (survivors, $n = 5$) and those who did not (non-survivors, $n = 24$). The two groups were compared.

Results: Overall survival rates at 1, 3 and 5 years were 62.1%, 24.1% and 17.2%, respectively. Four (80.0%) 5-year survivors had recurrences of HCC in which the number of recurrent nodules was under four. Three (21.4%) of the 14 non-survivors who underwent curative resection experienced recurrences of HCC and all of them demonstrated fewer than four recurrent nodules ($P = 0.0114$). Local therapy, such as radiofrequency ablation and resection of recurrence, had more often been used in survivors than in non-survivors ($P = 0.0364$).

Conclusions: Although surgical outcomes in patients with HCC accompanied by MPVTT are unsatisfactory, some patients do enjoy longterm survival. When the number of recurrent nodules is less than four, local therapy should be selected with the aim of achieving 5-year survival.

Keywords

hepatocellular carcinoma, main portal vein tumour thrombus, hepatic resection, recurrent pattern, local therapy, longterm survival

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Introduction

Hepatocellular carcinoma (HCC) is one of the most malignant diseases in the world.[1] In particular, HCC with tumour thrombus in the first branch of the portal vein (Vp3) or with tumour thrombus in the main portal trunk or the opposite side portal branch (Vp4) is considered to represent an end-stage condition with a poor prognosis because tumour cells are likely to have spread throughout the liver.[2] In recent reports,[3,4] HCC patients with main portal vein tumour thrombus (MPVTT) are described as surviving only 2.7–4.0 months if left untreated. Hepatic resection remains the only potentially curative treatment for such patients. However, in patients who undergo hepatic resection for HCC with MPVTT (Vp3 and Vp4), postoperative 5-year survival rates are only 10–30%.[5–9] Nevertheless, there are a few 5-year survivors. Ikai *et al.*[5] reported a 5-year survival rate of 10.9% (four patients) and Le Treut *et al.*[6] reported the 5-year survival of two of 22 patients with HCC accompanied by MPVTT.

This study retrospectively investigated the clinical and pathological characteristics of 29 HCC patients with MPVTT in an attempt to clarify the factors determining 5-year survival in patients with HCC accompanied by MPVTT.

Materials and methods

Patients

This study included 692 HCC patients who underwent liver resection between 1985 and 2005 at the Department of Surgery and Science, Kyushu University Hospital. Preoperative ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), angiography and CT during angiography were performed in all patients. From a retrospective database, 29 patients (4.2%) with tumour invasion of the first branch of the portal vein (Vp3) and tumour in the main portal trunk or the opposite side portal branch (Vp4) were enrolled in this study. These included 25 male and four female patients with a median age of 55 years (range: 29–76 years). Among these patients, 12 (41.4%) were infected with hepatitis C virus (HCV) and 16 (55.2%) with hepatitis B virus (HBV). The median finding on the indocyanine green retention test at 15 min ($ICGR_{15}$) was 11.4% (range: 1.4–33.6%).

Methods

The 29 patients were divided into two groups consisting of those who survived for >5 years after hepatectomy (5-year survivors, $n = 5$) and those who did not (non-survivors, $n = 24$). Possible preoperative prognostic factors investigated in both groups included age, sex, HBV surface antigen, anti-HCV antibody, $ICGR_{15}$ result, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alpha fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP). Various cancer-related factors including maximum tumour size, tumour grade (good, moderate or poor) and the presence of intrahepatic metastases were also examined. Our institutional review board approved the study protocol, which conformed to the Helsinki Declaration of 1975.

Operative procedures

Hepatic resection procedures included one trisegmentectomy, 27 lobectomies (11 left, 16 right) and one segmentectomy. There were no significant differences between the two groups in surgical procedures. Curative resection was defined as hepatic resection with no residual HCC. Inoue *et al.*[10] reported no differences in outcome between the peeling-off technique (in which the MPVTT is resected but the portal vein thrombus-bearing territory is preserved) and the en bloc technique (in which the portal veins are reconstructed) when these were performed in association with thrombectomy. All surgery in this study employed the peeling-off technique.

Patient follow-up

Follow-up of patients after hepatectomy followed a strict protocol, which did not change during the study period. Patients were examined for recurrence by US and tumour markers such as AFP and DCP every month and by CT every 3 months.

Recurrence after curative resection

Recurrence of HCC was examined in the 19 patients who had undergone curative resection of primary HCC. Of these 19 patients, 18 had postoperative recurrence of HCC. The recurrence pattern and therapy for recurrence were examined. The recurrence pattern was analysed according to the number of recurrent nodules. This number included metastatic nodules in sites other than the liver. Patients with HCC recurrence were divided into two groups comprising, respectively, those with four or more recurrent nodules and those with fewer than four recurrent nodules.

The therapeutic modalities for recurrent HCC were resection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), regional chemotherapy and radiation. Repeat hepatectomy for recurrent HCC in the liver was the treatment of choice until recently, when local ablation therapy was recommended as the initial treatment when the recurrent tumour measured <2 cm in diameter and no more than three intrahepatic nodules were found.[11] Although all patients in this study had MPVTT, those with intrahepatic recurrence of HCC were treated according to the strategy described above, using local therapy, such as resection and RFA, when possible. In patients with distant metastases, pulmonary and bone metastases were resected if resection was possible, the metastases numbered less than four and intrahepatic recurrence was under control.

Statistical analysis

All data are expressed as median value. Independent chi-squared tests were used for categorical variables. Continuous variables were compared by unpaired Student's *t*-tests. Cumulative and disease-free survival rates were obtained using the Kaplan–Meier method. Differences in survival between groups were compared for each variable using the log-rank test. The starting point for the calculation of survival time was the date of operation. Death, including deaths that were cancer- or liver-related, represented the end-point. A *P*-value of <0.05 was considered to indicate statistical significance.

Results

The median length of follow-up was 36 months (range: 18 days to 234 months). One patient died of operative morbidity. Overall survival rates at 1, 3 and 5 years were 62.1%, 24.1% and 17.2%, respectively (Fig. 1). The median survival time in all 29 patients was 16.6 months.

Table 1 compares clinical and pathological variables in 5-year survivors ($n = 5$) and non-survivors ($n = 24$). Preoperative serum concentrations of DCP in 5-year survivors were significantly lower than in non-survivors ($P = 0.0052$). In 19 patients, curative resection (no residual HCC nodules) was performed. Non-curative resection with residual HCC was performed in 10 patients. Overall survival rates at 1, 3 and 5 years were 73.4%, 36.8% and 26.3%, respectively, in patients who underwent curative resection and 38.5%, 0% and 0%, respectively, in those who underwent non-curative resection (Fig. 2). All of the 5-year survivors had undergone curative resection. All of the patients

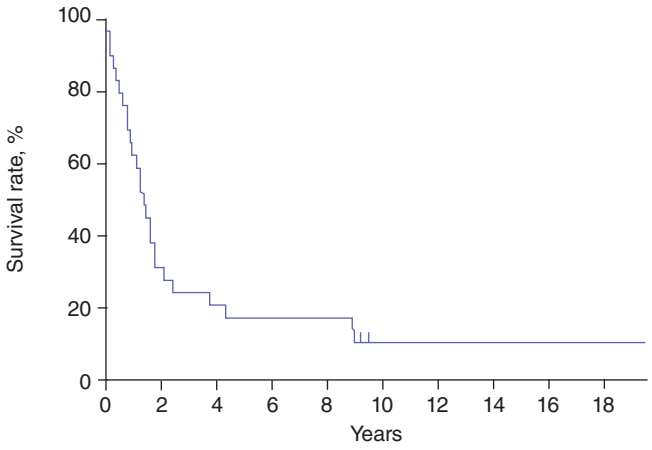

Figure 1 Overall survival rates after hepatic resection in patients with hepatocellular carcinoma accompanied by main portal vein tumour thrombus ($n = 29$)

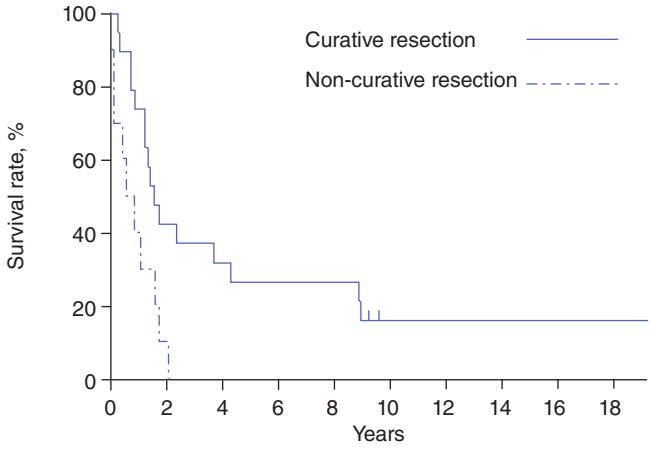

Figure 2 Comparison of overall survival in patients who underwent curative ($n = 19$) vs. non-curative ($n = 10$) resection ($P = 0.1336$)

Table 1 Comparison of clinicopathological factors in non-survivors and 5-year survivors

Factor	Non-survivors ($n = 24$)	5-year survivors ($n = 5$)	*P*-value
Gender, male, *n* (%)	21 (87.5%)	4 (80.0%)	0.3896
Age, years, median (range)	56 (29–76)	51 (49–63)	0.3896
Total bilirubin, mg/dl, median (range)	0.9 (0.4–4.0)	1.1 (0.5–1.4)	0.3133
Albumin, g/dl, median (range)	3.7 (3.1–4.9)	3.8 (3.1–4.3)	0.5346
AST, U/l, median (range)	65 (19–1160)	36 (22–78)	0.0365[a]
ALT, U/l, median (range)	48 (10–338)	37 (25–300)	0.5913
Positive HBVs-Ag, *n*(%)	13 (54.2%)	3 (60.0%)	1.0000
Positive HCV-Ab, *n* (%)	9 (37.5%)	3 (60.0%)	0.6221
AFP, ng/ml, median (range)	4 001 (7–422 680)	2 325 (152.1–98 030)	0.1914
DCP, mAU/ml, median (range)	4 240 (24–75 000)	1 210 (18–2028)	0.0052[a]
DCP <2200 mAU/ml, *n* (%)	10 (41.7%)	5 (100%)	0.0421[a]
$ICGR_{15}$, %, median (range)	12.0 (5.5–33.6)	8.7 (1.4–24.5)	0.1456
Main tumour size, cm, median (range)	8.5 (2.0–16.0)	3.9 (2.2–13.0)	0.1463
Tumour differentiation, moderate, *n* (%)	4 (16.7%)	2 (40.0%)	0.2709
Intrahepatic metastasis, *n* (%)	23 (95.8%)	3 (60.0%)	0.0684
Surgical curability, *n* (%)	14 (58.3%)	5 (100%)	0.1336
Blood loss, ml, median (range)	1 900 (493–23 000)	1 800 (1800–12 500)	0.5198
Transfusion rate, %	41.7%	40.0%	1.0000

[a]$P < 0.05$.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBVs-Ag, hepatitis B virus surface antigen; HCV-Ab, hepatitis C virus antibody; AFP, alphafetoprotein; DCP, des-γ-carboxy prothrombin; $ICGR_{15}$, indocyanine green retention test at 15 min.

who underwent non-curative resection died within 2 years of surgery. The difference in survival rates is not statistically significant ($P = 0.1336$).

Overall survival in patients with high and low serum concentrations of DCP (≥2200 mAU/ml and <2200 mAU/ml, respectively) was examined. The difference was statistically significant ($P = 0.0421$). Disease-free survival in patients who underwent curative resection is shown in Fig. 3. All except one of the 5-year survivors had postoperative recurrence. There was no significant difference in disease-free survival between 5-year survivors and non-survivors. Recurrence patterns in the two groups are compared in Table 2. Of 18 patients in whom HCC recurred after curative resection, seven (38.8%) patients demonstrated less than four nodules. Clear differences in recurrence patterns were observed between the two groups. All of the 5-year survivors showed fewer than four recurrent nodules, whereas only 21.4% of

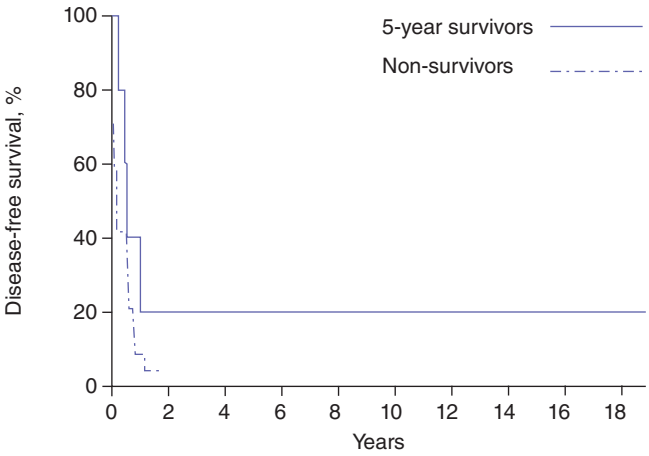

Figure 3 Comparison of disease-free survival in 5-year survivors (n = 5) and non-survivors (n = 24) after curative resection (P = 0.1134)

non-survivors showed fewer than four recurrent nodules (P = 0.0114). The most common organ in which recurrence occurred was the liver; other sites of recurrence included lung, bone, brain and peritoneum.

Statistically significant differences between the two groups in the therapeutic modalities used for recurrent HCC emerged. Local therapy, such as resection and RFA for recurrent nodules, was performed more commonly in the 5-year survivors than in the non-survivors (P = 0.0364).

Discussion

The prognosis of HCC patients with MPVTT is extremely poor, even after the application of various therapeutic modalities, and the optimal treatment of these patients remains controversial. In previous reports, realistic therapeutic options have included TACE, regional chemotherapy and radiation.[12] Mean survival times and response rates are <10 months and ≤40%, respectively, in patients who undergo TACE.[13–16] With regional chemotherapy, although much higher response rates, such as 63%, have been reported, mean survival times are <1 year.[17–23] Radiation therapy gives much higher response rates, which can reach as much as 100%, but the maximum median survival time reported is 10.7 months.[24–29] Thus, median survival time is <12 months in patients who undergo therapeutic modalities other than surgery. In hepatic resection, 5-year survival rates of 0–22.4% (Table 3) and median survival times of 6.4–20.0 months have been reported.[5–9] The current study found a 5-year survival rate of 17.4% and a median survival of 16.6 months. These results suggest that hepatic resection may represent the treatment of choice in patients with HCC and MPVTT.

Reports of longterm survival are extremely rare in patients with HCC accompanied by MPVTT. Numbers of 5-year survivors in previous reports are shown in Table 3. These numbers are extremely small and the factors that enable 5-year survival remain unclear. In this study, preoperative serum concentrations of DCP were significantly lower in 5-year survivors and all the 5-year survivors underwent curative resection (no residual HCC). In this study, the crucial cut-off point for serum concentrations of DCP seems to be <2200 mAU/ml. A DCP has been reported to represent a poor prognostic factor in patients with HCC undergoing hepatic resection[30,31] or liver transplantation[32,33] and is reportedly associated with microvascular invasion by HCC cells.[34] In this study, all patients had portal vein invasion; therefore other mechanisms must be presumed to have had effect. Recently, Yue *et al.*[35] showed that DCP induces matrix metalloproteinase activity in HCC cells and Wang *et al.*[36] showed that DCP induces human vascular endothelial cell growth and migration. Fujikawa *et al.*[37] showed that HCC arterial vascularity strongly correlates with expression of serum and tissue DCP, and suggested DCP secreted from HCC cells may not act as a paracrine interaction factor between HCC and vascular endothelial cells, but as an autocrine driver. Recently, Murata *et al.*[38] showed that cytoskeletal changes during epithelial mesenchymal transition serve as a crucial mechanism for DCP production in HCC. These findings suggest that DCP may influence the malignant potential of HCC cells by mechanisms other than vessel invasion.

Recurrence of HCC after hepatectomy and thrombectomy occurs in most patients with MPVTT and is usually difficult to control once it has occurred. The presence of HCC with MPVTT has been considered to represent an end-stage condition with a poor prognosis because tumour cells are likely to have spread throughout the liver. However, the number of recurrent nodules seems to be an important determinant of 5-year survival. In this study, sites of recurrence in 5-year survivors included distant metastatic sites, such as lung and bone. This suggests that the recurrence of fewer than four nodules is not always associated with further multiple recurrences. Therefore, in patients with fewer than four recurrent nodules, local therapy may prolong survival. In this study, two of the 5-year survivors underwent resection of distant metastases, one underwent repeat hepatectomy and one underwent RFA for intrahepatic recurrence. After the local therapy, two patients remained free from HCC recurrence for >5 years. Therefore, in patients with fewer than four recurrent nodules, local therapy such as resection and/or ablation therapy may prolong survival. Thus, when the number of recurrent nodules is under four, local therapy should be selected with the aim of achieving 5-year survival. The effectiveness of surgical resection for pulmonary metastases from HCC after hepatectomy has been shown previously.[39] It is crucial to understand that local therapy can be useful for recurrence after curative resection, even in patients with MPVTT.

The prognosis remains extremely poor in patients who undergo non-curative resection and demonstrate four or more recurrent nodules. It is clear that other therapeutic strategies are necessary. Regional chemotherapy, including interferon-α (IFN-α) may be another option for adjuvant therapy after surgery. Nagano[40]

Table 2 Comparison of recurrence patterns and therapeutic modalities for recurrent hepatocellular carcinoma in curatively resected patients (n = 19)

Analysis of recurrence	Non-survivors (n = 14)	5-year survivors (n = 5)	P-value
Recurrence, n (%)	14 (100%)	4 (80.0%)	
Number of nodules in recurrence, n (%)			
<4	3 (21.4%)	4 (100%)	0.0114
≥4	11 (78.6%)	0	
Sites of recurrence, n			
Liver	13	3	
Lung	1	1	
Bone	1	1	
Brain	1	0	
Peritoneum	1	0	
Treatment for the first recurrence, n			0.0364
Resection	0	2	
Radiofrequency ablation	3	1	
TACE (+ radiation)	8	1	
Best supportive care	3	0	

TACE, transarterial chemoembolization.

Table 3 Recent reports on outcomes in patients with hepatocellular carcinoma (HCC) accompanied by portal vein tumour thrombus

Author(s)	Published	Setting	Patients (Vp3 and Vp4), n	Median survival, months	5-year survival, % (Kaplan-Meier)	5-year survivors, n
Ikai *et al*.[5]	2006	HCC with MPVTT (Vp3 and Vp4)	78	6.9	10.9%	4
Le Treut *et al*.[6]	2006	Tumour thrombus in portal and hepatic veins (n = 26)	22	9.0	17.0%	2
Kondo *et al*.[7]	2009	HCC with MPVTT (Vp1–4, n = 48)	29	11.3	0% (only Vp4)	0
Ban *et al*.[8]	2009	HCC with MPVTT (Vp3 and Vp4)	45	20.0	22.4%	3
Shi *et al*.[9]	2010	HCC with MPVTT (Vp1–4, n = 406)	98	6.4	0% (only Vp4)	0
Present study	2011	HCC with MPVTT (Vp3 and Vp4)	29	16.9	17.2%	5

Vp3, first branch of the portal vein; Vp4, main portal trunk or the opposite portal branch.

demonstrated that adjuvant chemotherapy with IFN-α and 5-fluorouracil (5-FU) is useful and prolongs survival. In HCC patients with MPVTT in whom curative resection cannot be performed, IFN-α and 5-FU therapy is effective and curative resection sometimes becomes possible after this therapy.[41] The combination of IFN-α and 5-FU therapy and hepatic resection may represent a promising strategy. The effects of sorafenib, a newly developed biologic therapy for non-resectable HCC, should be clarified in these patients.[42]

In conclusion, factors that relate positively to 5-year survival after hepatic resection seem to be low serum concentrations of DCP and curative resection. In patients who show recurrence of HCC, the presence of fewer than four recurrent nodules seems to be a good predictor of longterm survival. Local therapy, such as surgical resection and/or ablation therapy, may be useful for this type of recurrence. Further therapeutic strategies are necessary in patients with high serum concentrations of DCP, who cannot undergo curative resection and have four or more recurrent nodules.

Conflicts of interest

None declared.

References

1. Okuda K. (1992) Hepatocellular carcinoma: recent progress. *Hepatology* 15:948–963.
2. Liver Cancer Study Group of Japan. (2003) *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer*, 2nd English edn. Tokyo: Kanehara.
3. Llovet JM, Bustamante J, Castelle A, Vilana R, Ayuso Mdel C, Sala M *et al*. (1999) Natural history of untreated non-surgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 29:62–67.

4. Villa E, Moles A, Ferreti I, Buttafoco P, Grottola A, Del Buono M *et al*. (2000) Natural history of inoperable hepatocellular carcinoma: oestrogen receptors' status in the tumour is the strongest prognostic factors for survival. *Hepatology* 32:233–238.
5. Ikai I, Hatano E, Hasegawa S, Fujii H, Taura K, Uyama N *et al*. (2006) Prognostic index for patients with hepatocellular carcinoma combined with tumour thrombosis in the major portal vein. *J Am Coll Surg* 202:431–438.
6. Le Treut YP, Hardwigsen J, Ananian P, Saïsse J, Grégoire E, Richa H *et al*. (2006) Resection of hepatocellular carcinoma with tumour thrombus in the major vasculature. A European case–control series. *J Gastrointest Surg* 10:855–862.
7. Kondo K, Chijiwa K, Kai M, Otani K, Nagaike K, Ohuchida J *et al*. (2009) Surgical strategy for hepatocellular carcinoma patients with portal vein tumour thrombus based on prognostic factors. *J Gastrointest Surg* 13:1078–1083.
8. Ban D, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y *et al*. (2009) Efficacy of a hepatectomy and a tumor thrombectomy for hepatocellular carcinoma with tumor thrombus extending to the main portal vein. *J Gastrointest Surg* 13:1921–1928.
9. Shi J, Lai E, Li N, Guo W, Xue J, Lau W *et al*. (2010) Surgical treatment of hepatocellular carcinoma with portal vein tumour thrombus. *Ann Surg Oncol* 17:2073–2080.
10. Inoue Y, Hasegawaw K, Ishizawa T, Aoki T, Sano K, Beck Y *et al*. (2009) Is there any difference in survival according to the portal vein thrombectomy method in patients with hepatocellular carcinoma? *Surgery* 145:9–19.
11. Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H, Maehara Y. (2011) Improvement of longterm outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. *World J Surg* 35:1072–1084.
12. Miyagawa M, Makuuchi M. (2006) Treatment of hepatocellular carcinoma accompanied by portal vein thrombus. *World J Gastroenterol* 12:7561–7567.
13. Okazaki M, Higashihara H, Koganemaru HE. (1991) Transcatheter arterial embolization for inoperative hepatocellular carcinoma. *Jpn J Clin Radiol* 36:535–539.
14. Chung JW, Park JH, Han JK, Choi BI, Han MC. (1995) Hepatocellular carcinoma and portal vein invasion: results of treatment with transcatheter oily chemoembolization. *AJR Am J Roentgenol* 165:315–321.
15. Georgiades CS, Hong K, D'Angelo M, Geschwind JF. (2005) Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 16:1653–1659.
16. Raoul JL, Guyader D, Bretagne JF, Duvauferrier R, Bourguet P, Bekhechi D *et al*. (1994) Randomized controlled trial for hepatocellular carcinoma with portal vein thrombosis: intra-arterial iodine-131-iodized oil versus medical support. *J Nucl Med* 35:1782–1787.
17. Ando E, Yamashita F, Tanaka M, Tanigawa K. (1997) A novel chemotherapy for advanced hepatocellular carcinoma with tumour thrombosis of the main trunk of the portal vein. *Cancer* 79:1890–1896.
18. Itamoto T, Nakahara H, Tashiro H, Haruta N, Asahara T, Naito A *et al*. (2002) Hepatic arterial infusion of 5-fluorouracil and cisplatin for unresectable hepatocellular carcinoma with tumour thrombus of the portal vein. *J Surg Oncol* 80:143–148.
19. Yamasaki T, Kurokawa H, Shirahashi H, Kuwano N, Hironaka K, Masuhara M *et al*. (2002) Novel arterial infusion chemotherapy using cisplatin, 5-fluorouracil, and leucovorin for patients with advanced hepatocellular carcinoma. *Hepatol Res* 23:7–17.
20. Urabe T, Kaneko S, Matsushita E, Unoura M, Kobayashi K. (1998) Clinical pilot study of intrahepatic arterial chemotherapy with methotrexale, 5-fluorouracil, cisplatin and subcutaneous interferon-alpha-2b for patients with locally advanced hepatocellular carcinoma. *Oncology* 55:39–47.
21. Kaneko S, Urabe T, Kobayashi K. (2002) Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. *Oncology* 62 (Suppl. 1):69–73.
22. Ota H, Nagano H, Sakon M, Eguchi H, Kondo M, Yamamoto T *et al*. (2005) Treatment of hepatocellular carcinoma with main portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil; role of type 1 interferon receptor expression. *Br J Cancer* 93:557–564.
23. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S *et al*. (2006) Combination therapy of intra-arterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal vein invasion. *Cancer* 106:1990–1997.
24. Tazawa J, Maeda M, Sakai Y, Yamane M, Ohbayashi H, Kakinuma S *et al*. (2001) Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. *J Gastroenterol Hepatol* 16:660–665.
25. Ishikura S, Ogino T, Furuse J, Satake M, Baba S, Kawashima M *et al*. (2002) Radiotherapy after transcatheter arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumour thrombus. *Am J Clin Oncol* 25:189–193.
26. Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E *et al*. (2003) Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumour thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 57:113–119.
27. Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH *et al*. (2005) A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or interior vena cava tumour thrombus. *Int J Radiat Oncol Biol Phys* 61:432–443.
28. Kim DY, Park W, Lim DH, Lee JH, Yoo BC, Paik SW *et al*. (2005) Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. *Cancer* 103:2419–2426.
29. Hata M, Tokuuye K, Sugahara S, Kagei K, Igaki H, Hashimoto T *et al*. (2005) Proton beam therapy for hepatocellular carcinoma with portal vein tumour thrombus. *Cancer* 104:794–801.
30. Shimada M, Takenaka K, Fujiwara Y, Gion T, Kajiyama K, Maeda T *et al*. (1996) Des-gamma-carboxy prothrombin and alpha-fetoprotein positive status as a new prognostic indicator after hepatic resection for hepatocellular carcinoma. *Cancer* 78:2094–2100.
31. Itoh S, Morita K, Ueda S, Sugimachi K, Yamashita Y, Gion T *et al*. (2009) Longterm results of hepatic resection combined with intraoperative local ablation therapy for patients with multinodular hepatocellular carcinomas. *Ann Surg Oncol* 16:3299–3307.
32. Taketomi A, Sanefuji K, Soejima Y, Yoshizumi T, Uhciyama H, Ikegami T *et al*. (2009) Impact of des-gamma-carboxy prothrombin and tumour size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. *Transplantation* 87:531–537.
33. Fujiki M, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S *et al*. (2009) Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. *Am J Transplant* 9:2362–2371.

34. Shirabe K, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S *et al*. (2007) The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol* 95:235–240.

35. Yue P, Gao ZH, Xue X, Cui SX, Zhao CR, Yuan YI *et al*. (2011) Des-γ-carboxyl prothrombin induces matrix metalloproteinase activity in hepatocellular carcinoma cells by involving the ERK 1/2 MAPK signalling pathway. *Eur J Cancer* 47:1115–1124.

36. Wang SB, Cheng YN, Cui SX, Zhong JL, Ward SG, Sun LR *et al*. (2009) Des-γ-carboxyl prothrombin stimulates human vascular endothelial cell growth and migration. *Clin Exp Metastasis* 26:469–477.

37. Fujikawa T, Shihara H, Yamamoto K. (2009) Significance of des-gamma-carboxy proliferation production in hepatocellular carcinoma. *Acta Med Okayama* 63:299–304.

38. Murata K, Suzuki H, Okano H, Oyamada T, Yasuda Y, Sakamoto A. (2009) Cytoskeletal changes during epithelial-to-fibroblastoid conversion as a crucial mechanism of des-gamma-carboxy prothrombin production in hepatocellular carcinoma. *Int J Oncol* 35:1005–1014.

39. Tomimaru Y, Sasaki Y, Yamada T, Eguchi H, Takami K, Ohigashi H *et al*. (2006) The significance of surgical resection for pulmonary metastasis from hepatocellular carcinoma. *Am J Surg* 192:46–51.

40. Nagano H. (2010) Treatment of advanced hepatocellular carcinoma: intra-arterial infusion chemotherapy combined with interferon. *Oncology* 78 (Suppl. 1):142–147.

41. Yamamoto T, Nagano H, Imai Y, Fukuda K, Matsumoto H, Kondo M *et al*. (2007) Successful treatment of multiple hepatocellular carcinoma with tumour thrombi in the major portal vein branches by intra-arterial 5-fluorouracil perfusion chemotherapy combined with subcutaneous interferon-alpha and hepatectomy. *Int J Clin Oncol* 12:150–154.

42. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF *et al*. (2008) Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 359:378–390.